

Competitive balance of intrabulge BMP/Wnt signaling reveals a robust gene network ruling stem cell homeostasis and cyclic activation.

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Public Summary:

Analyses reveals intra-Hair follicle Stem Cells gene regulatory network with feed-back control between activators and inhibitors. The robust molecular circuits allows for a constant competitive balance between BMP and WNT signaling. BMP inhibition regulates ligand-receptor dependent canonical Wnt activation. The self-regulatory nature allows activation and quiescence of stem cells to occur in a cyclic way during physiological conditions, response to injury, and protection against tumorigenesis when over-activated.

Scientific Abstract:

Hair follicles facilitate the study of stem cell behavior because stem cells in progressive activation stages, ordered within the follicle architecture, are capable of cyclic regeneration. To study the gene network governing the homeostasis of hair bulge stem cells, we developed a Keratin 15-driven genetic model to directly perturb molecular signaling in the stem cells. We visualize the behavior of these modified stem cells, evaluating their hair-regenerating ability and profile their molecular expression. Bone morphogenetic protein (BMP)-inactivated stem cells exhibit molecular profiles resembling those of hair germs, yet still possess multipotentiality in vivo. These cells also exhibit up-regulation of Wnt7a, Wnt7b, and Wnt16 ligands and Frizzled (Fzd) 10 receptor. We demonstrate direct transcriptional modulation of the Wnt7a promoter. These results highlight a previously unknown intra-stem cell antagonistic competition, between BMP and Wnt signaling, to balance stem cell activity. Reduced BMP signaling and increased Wnt signaling tilts each stem cell toward a hair germ fate and, vice versa, based on a continuous scale dependent on the ratio of BMP/Wnt activity. This work reveals one more hierarchical layer regulating stem cell homeostasis beneath the stem cell-dermal papilla-based epithelial-mesenchymal interaction layer and the hair follicle-intradermal adipocyte-based tissue interaction layer. Although hierarchical layers are all based on BMP/Wnt signaling, the multilayered control ensures that all information is taken into consideration and allows hair stem cells to sum up the total activators/inhibitors involved in making the decision of activation.

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